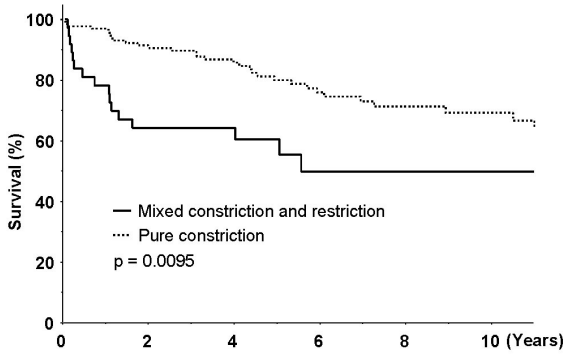
1109-134 **Clinical Features of Mixed Physiology of Constriction and Restriction**

Hirotsugu Yamada, Tomotsugu Tabata, Jeanne K. Drinko, Susan E. Jasper, Michael S. Lauer, James D. Thomas, Allan L. Klein, Cleveland Clinic Foundation, Cleveland, OH

Background: Patients with mixed physiology of constriction and restriction have been reported, but their long-term survival has not been well documented.
***Methods*:** Study subjects consisted of 38 patients (57 ± 14 yrs, 8 female, 30 male) who were diagnosed as having mixed physiology based on echocardiography, MRI (or CT), cardiac catheterization, endomyocardial biopsy and/or surgical findings. We evaluated their echocardiographic, clinical features and calculated Kaplan-Meier survival curve to compare with that in patients with pure constriction.
Results: Prior radiation therapy was the most frequent (50%) cause of mixed physiology followed by coronary artery bypass graft without prior radiation and heart transplantation. The respiratory variation of peak early diastolic transmitral flow velocity was 10.7% in patients with sinus rhythm, 18.1% in patients with atrial arrhythmia. Pericardial thickening was localized in 29 patients. All-cause 5-year mortality was 40 % and unrelated to age, etiology, left ventricular systolic function and therapeutic course. There was a significant difference between the survival rates in patients with mixed physiology and in 133 patients with pure constriction (Figure).
***Conclusions*:** Because of the high mortality in mixed disease, discrimination of this entity from pure constriction is important. Echocardiography is helpful noninvasive technique in diagnosis and understanding the physiology of the patients with mixed constriction and restriction.



ORAL CONTRIBUTIONS

834 Dilated Cardiomyopathy: Basic and Clinical II

Tuesday, March 09, 2004, 8:30 a.m.-10:00 a.m.
Morial Convention Center, Room 217

8:30 a.m.

834-1 **Vascular and Autonomic Dysfunction in the Asymptomatic Stage of Chagas's Disease**

Juan C. Guzman, Hernando Leon, Ronald G. Garcia, Juan P. Casas, Federico A. Silva, Patricio Lopez-Jaramillo, Carlos A. Morillo, Fundacion Cardiovascular de Colombia, Floridablanca, Colombia

Background: Chagas' Disease (ChD) is associated with impaired cardiac automic function (CAF) and altered peripheral endothelial vascular reactivity. The relationship between these two alterations has not been explored in the early asymptomatic stage of ChD.
Methods: 22 asymptomatic seropositive subjects to ChD were compared with 19 asymptomatic seronegative subjects (CON). All patients had a noninvasive assessment of CAF: deep breathing test (DBT), arterial baroreflex (BRS) and lower body negative pressure @ -10mmHg (LBNP) and endothelial function measured by forearm blood flow (FBF), peripheral vascular resistance (PVR) and venous occlusion plethysmography with vasoactive substances: nitroglycerine (NTG) and acetylcholine (Ach)
Results No significant differences were found between the two groups at baseline. A significant reduction was found ($p<0.01$) in the BRS 17.6±8.3 vs 28.3±14.1 and DBT 11.0 ±5.7 vs 17.2 ±7.2 in ChD patients vs CON. Significant differences were found between ChD vs CON in FBF at rest;1.4±0.4vs.2.3±0.7 ($p<0.001$) and during LBNP;1.0±0.3vs.1.5±0.6. Moreover significant differences were found in PVR at rest 65.3±20.2 vs 41.1±15.4 ($p<0.05$), LBNP 103.7±26.6 vs 71.8±43.01. ChD group had lower response than CON in terms of percentage of change of FBF in response to the infusion of incremental dosages of NTG: 8 nmoll/min 49.7±34.5 vs. 82.7±58.0; 16 nmol/min 62.2±43.5 vs 159.6±83.6; 34 nmol/min 77.9±54.8 vs 197.13±10.8.5 and with Ach 25 nmol/min 88.4±57 vs 172.8±104; 50 nmol/min 103.1±46 vs 172.7±128; 100 nmol/min 125.3±93 vs 210.5±123.
Conclusion: Asymptomatic ChD patients have early impairment of vascular endothelial function mediated by an increase in efferent sympathetic activity that leads to elevated PVR. These findings may be related to alterations in the endothelial production of nitric oxide and lower vascular smooth muscle response to NO. These alterations may play a role in precipitating and maintaining the progressive damage of myocardial microvasculature and contribute to the development and progression of the Chagasic cardiomyopathy.
(Colciencias Grant: 6566-04-10268)

8:45 a.m.

834-2 **Clonal T-Cell-Receptor Composition Is Not Associated With Enteroviral or Adenoviral Infection in Dilated Cardiomyopathy: Implications for the Pathogenesis of Dilated Cardiomyopathy**

Michel Noutsias, Michael Hummel, Chalid Assaf, Harald Stein, Uwe Kuhl, Heinz Peter Schultheiss, Matthias Pauschinger, Charité - Campus Benjamin Franklin, Berlin, Germany

Background: Autoimmunity, resulting from molecular mimicry between viral and cryptic cardiac antigens, is postulated for the pathogenesis of dilated cardiomyopathy (DCM). Autoimmunity targeting distinct antigens evokes expansion of specifically reactive T-cell clones infiltrating the target tissue, which can also result from chronic presentation of foreign (e.g. viral) antigens.
Methods: DNA extracted from explanted DCM hearts (n=17, 1 female; 49±13 years; LVEF: 18±5%) were investigated by a family specific PCR for the Vß-N-Dß-N-Jß-region of the TCR gene and GeneScan-analysis for clonal TCR rearrangement. Non-DCM-hearts (ischaemic cardiomyopathy: n=2, valvular heart disease: n=3, donor hearts: n=3) served as controls. The TCR-PCR-products analyzed by high-resolution fragment analysis (GeneScan), displayed a Gaussian-like distribution profiles in polyclonal and single dominant peaks in monoclonal T-cell populations. Clonal TCR-ß PCR-products were directly sequenced. Enteroviral and adenoviral genome was amplified by PCR.
Results: The GeneScan analysis of the TCR-ß PCR-products demonstrated a clonal T-cell population in n=9/17 (53%) of the DCM hearts. In contrast, exclusively polyclonal composition of the TCR-Vß PCR-products were obtained from the non-DCM hearts. Sequence analysis of the clonal TCR-Vß PCR-products from the n=9 DCM hearts determined Vß19.01 in n=6 cases (67%), and Vß6-1.01, Vß6-3.01 and Vß10-3.04 in each of the remaining cases. Clonal TCR-composition was not significantly ($p>0.05$) associated with PCR amplification of viral genome.
Conclusions: Clonal TCR rearrangement is exclusively present in DCM but not in further cardiomyopathies. The clear predominance of Vß19.01 family T-cell clones in DCM indicates that these TCR clones target specific antigens. Our results are consistent with the autoimmune hypothesis of DCM, since entero- or adenoviral persistence are not significantly associated with a specific clonal TCR rearrangement. Eventually, a TCR-based immunotherapy in DCM (e.g. with anti-TCR antibodies or DNA vaccines) might be a feasible therapeutic option in DCM with clonal TCR-composition.

9:00 a.m.

834-3 **Impaired Hyperaemic Myocardial Blood Flow Is Related to Systolic Function in Idiopathic Dilated Cardiomyopathy**

Paul Knaapen, MWJ Götte, JJM Zwanenburg, JT Marcus, P. A. Dijkmans, WG van Dockum, CA Visser, AC van Rossum, AA Lammertsma, FC Visser, VU University Medical Center, Amsterdam, The Netherlands

Aim. Hyperaemic myocardial blood flow is impaired in patients with idiopathic dilated cardiomyopathy (DCM). The degree of impairment is related to diastolic dysfunction and prognosis. This study was conducted to evaluate the relation between hyperaemic myocardial blood flow and systolic function in patients with DCM.
Materials & Methods. Patients with advanced stage of idiopathic dilated cardiomyopathy (NYHA III or IV; EF<35%) and healthy control subjects were studied. Myocardial blood flow (MBF) was determined by positron emission tomography (PET) using ^{15}O-labelled water under baseline conditions and during pharmacologically induced stress. MR tissue tagging was performed for quantification of regional myocardial function. End systolic circumferential shortening (ESCS) was calculated using the Harmonic Phase (HARP) method.
Results. Ten patients with DCM (mean age 54±10 yrs, 5 male) and 7 control subjects (mean age 28±3 yrs, 6 male) were studied. Mean rest MBF was similar for DCM and controls (0.91±0.33 vs. 0.97±0.21 ml/min/g, respectively, p=NS). Hyperaemic MBF and ESCS were reduced in DCM (2.23±1.01 ml/min/g and 6.1±2.4%, respectively) compared to controls (4.09±0.80 ml/min/g and 15.2±1.3%, respectively, $p<0.01$). There was a significant correlation between stress MBF and ESCS in DCM ($r=0.89$, $p<0.01$). No correlation was present between rest MBF and systolic function in DCM.
Conclusions. The combination of PET and MRI offers a unique opportunity to quantitatively assess global and regional perfusion and function. In patients with advanced stage of DCM, the degree of impaired hyperaemic blood flow is related to systolic dysfunction.

9:15 a.m.

834-4 **Coronary Vasodilator Responses Are Impaired Independent of Nitric Oxide and Endothelial Function in Conscious Dogs With Dilated Cardiomyopathy**

Lazaros A. Nikolaidis, Aaron Doverspike, Teresa Hentosz, Rhonda Huerbin, Richard P. Shannon, Allegheny General Hospital, Pittsburgh, PA

Background: Dilated cardiomyopathy (DCM) has been associated with nitric oxide (NO) deficiency and endothelial dysfunction, resulting in depressed systemic and coronary vasodilator responses to endothelium-dependent challenge. However, it remains controversial as to whether endothelium-independent vasomotor function is preserved in DCM,

particularly in the coronary circulation. We have shown previously that intrinsic smooth muscle tone in coronary vessels in DCM is depressed, but the functional significance of this observation in vivo is unknown.
Methods: We studied the responses of the systemic and coronary circulation to a variety of vasodilators in conscious dogs with pacing-induced DCM (240 min-1, 29±4 days). The dogs received graded IV infusions of the endothelium-dependent acetylcholine (ACH, 0.25-5 μg/kg, n=18), the c-GMP dependent NO-donor nitroglycerin (NTG, 30-240 μg, n=18), the predominantly endothelium-independent adenosine (ADO, 0.5-5 μmol/kg, n=9), the β-adrenergic c-AMP dependent agonist isoproterenol (ISO, 0.05-0.4 μg/kg, n=14) and the calcium channel antagonist nicardipine (NIC, 0.3-10 μmol/kg, n=6) in control (C) and in severe DCM.
Results: Systemic responses were impaired to ACH but preserved to all other vasodilators in DCM. However, coronary flow (CBF) and vasodilator responses (CVR) were significantly ($p< 0.05$) depressed to all agonists when equivalent doses were compared. (Peak CBF responses, C vs DCM: ACH: 221±14% vs 160±11%, NTG: 220±17% vs 138±9%, ADO: 635±74% vs 413±65%, NIC: 338±59% vs 115±23%, ISO: 219±19% vs 87±21%. Peak CVR responses, C vs DCM: ACH: -77±1% vs -69±1%, NTG: -75±1% vs -62±2%, ADO: -88±1% vs -77±3%, NIC: -79±2% vs -63±4%, ISO: -67±2% vs -48±5%). This generalized impairment in coronary vasodilator responses persisted after controlling for heart rate differences or changes in mean arterial pressure.
Conclusions: In contrast to systemic vasodilator responses, coronary vasodilation in DCM is impaired to a multitude of agonists, dependent or independent of NO or second messenger mechanisms. This implies structural or distal signaling defects unique to the coronary vascular smooth muscle in DCM.

9:30 a.m.

834-5 Outcomes of Peripartum Cardiomyopathy in the Current Era of Heart Failure Management

José A. Tallaj, Saema Mirza, Barry K. Rayburn, Laura J. Pinderski, Raymond L. Benza, Brian A. Foley, Salpy Pamboukian, Robert C. Bourge, University of Alabama at Birmingham, Birmingham, AL, Birmingham VA Medical Center, Birmingham, AL

Background: Patients with peripartum cardiomyopathy (PPC) have a better prognosis than other forms of cardiomyopathy. However, historical studies showed that 40 to 50% of patients with PPC do not have a meaningful recovery or experienced a significant deterioration in their cardiac function. These studies were done before the current era of heart failure management. We report the University of Alabama at Birmingham's experience with this form of cardiomyopathy.
Methods and Results: Thirty-seven patients were referred to our program with peripartum cardiomyopathy between January 1, 1990 and December 31, 2002. The data was extracted from the clinical charts. The age at diagnosis was 28±6.6 years, and on average patients were 33 days postpartum (range 60 days pre-180 days post-partum). Eighty-one percent were NYHA class III or IV. The mean LVEDD was 57.9±10.0 mm and the LVEF was 23.5±11.5%. Thirty-two (87%) were treated with ACE inhibitors, 9 (25%) with angiotensin receptor blockers and 17 (46%) with beta-blockers. In addition they were also treated with digoxin (76%), diuretics (89%), spironolactone (33%), nitrates (6%) and warfarin (41%).
Patients were followed for an average of 28 (range 1-94) months. Four patients were transplanted, 1 died and 1 was lost to follow-up. The NYHA class improved significantly (P=0.007). More importantly, the NYHA class improved in all but the patients who died or were transplanted or lost to follow-up. Of the survivals or not transplanted or lost to follow-up, 25/31 (90%) were NYHA class I-II and none was NYHA class IV. Thirty-one patients had follow-up echocardiograms in our institution. Overall, the LVEF improved significantly to 40.3±16.4% ($p<0.001$), as well as the LVEDD (52.8±8.8 mm, p=0.007). Seventy-two percent of the patients had a significant improvement in the LVEF to $\geq$ 40%, and 42% of patients normalized their LVEF. There was no difference in NYHA class, LVEF or transplant/death rates in patients who were treated with beta-blockers compared to whose who were not.
Conclusion: The prognosis of PPC appears to be better than previously reported. Transplantation or more invasive therapies should be reserved for those patients who fail medical therapy.

9:45 a.m.

834-6 Identification of Cardiac Sarcoidosis From the Patients Presenting as Unexplained Heart Failure and Cardiomyopathies

Osamu Yokoseki, Yoshikazu Yazaki, Kaoru Kogashi, Takeshi Hanaoka, Yuichi Kai, Osamu KInoshita, Minoru Hongo, Keishi Kubo, Morie Sekiguchi, Shinshu University, Matsumoto, Japan

Background: Diagnosis of cardiac sarcoidosis (CS) is usually confirmed during the follow-up of extra-cardiac sarcoidosis. However, the diagnosis is often difficult when CS patients show heart failure as the first manifestation without evidence of involvement of other organs because endomyocardial biopsy frequently fails to reveal non-caseating epithelioid granuloma. Majority of these patients are diagnosed as idiopathic dilated cardiomyopathy (DCM). **Methods**: To characterize CS patients presenting as unexplained heart failure (CS-HF), we reviewed 30 consecutive CS patients diagnosed between 1987 and 2002 and identified 11 CS-HF patients. Clinical findings and outcome of the CS-HF were compared to those of 123 DCM patients diagnosed at the same period. **Results**: Abnormal accumulation of gallium-67 in the heart or extra-cardiac tissue was the first clue to suspect CS in 7 of the 8 CS-HF who underwent the whole body gallium-67 scan. Granulomas were confirmed from the heart in 5 patients, lymph nodes in 4, skin in 1 and skeletal muscle in 1. The CS-HF showed higher incidence of female (70% vs. 22%, $p< 0.001$), complete atrioventricular block (70% vs. 0%, $p<0.0001$) and sustained ventricular tachycardia (40% vs. 9%, $p< 0.05$), and lower cardiac index (2.0±0.4 l/min/m2 vs. 2.5±0.5 l/min/m2, $p< 0.05$) and left ventricular dimension (58±11 mm vs. 68±8 mm, $p<0.05$) as compared with DCM patients. During a mean follow-up of 80 months, 6 CS-HF died suddenly or of refractory heart failure. Although 10 of the 11 were treated with corticosteroids, survival rate was significantly worse in CS-HF than DCM (40% vs. 72%, $p<0.001$).
Conclusions: CS-HF had different clinical features and outcomes as compared with DCM. Understanding these features and comprehensive examinations including whole body gallium-67 scan and biopsies from the extra-cardiac tissue are useful for the diagnosis of CS patients presenting as unexplained heart failure and cardiomyopathies.

ORAL CONTRIBUTIONS

835 Heart Failure: Clinical Trials

Tuesday, March 09, 2004, 8:30 a.m.-10:00 a.m.
Morial Convention Center, Room 257

8:30 a.m.

835-1 A Comparison of Adverse Events Occurring With Carvedilol or Metoprolol in the Treatment of Heart Failure: Results From COMET

Philip A. Poole-Wilson, Karl Swedberg, John G. Cleland, Andrea Di Lenarda, Peter Hanrath, Beatrix Lutiger, Michel Komajda, Marco Metra, Willem J. Remme, Armin Scherhag, Andrew Charlesworth, Christian Torp-Pedersen, For the COMET investigators, National Heart and Lung Institute, London, United Kingdom, Sahlgrenska University Hospital, Göteborg, Sweden

Background: In COMET carvedilol (25 mg bid) was shown to reduce mortality compared to metoprolol (IR 50 mg bid) (512 deaths/1511 versus 600/1518, p=0.0017) in the treatment of heart failure with a mean follow-up of 57.9 months. Adverse events would be expected to reflect this advantageous outcome. The alpha-1 and beta-2-blocking effects of carvedilol, which possibly contributed to its survival advantage, are expected to be reflected in the adverse events profile.
Methods: 3029 patients with left ventricular systolic dysfunction and NYHA class II to IV were randomised to double-blind study therapy. Patients were seen every four months over a period of 47 to 71 months. Adverse events as reported by the investigator were recorded on the case record form and analysed centrally.
Results: Of 1511 patients allocated to carvedilol 93.6% experienced an adverse event and 73.9% a cardiovascular adverse event. Of 1518 patients allocated metoprolol the figures were 95.9% and 75.8%. Adverse event reports of sudden death (8.9% versus 12.1%), myocardial infarction (4.6% versus 6.3%), unstable angina (3.8% versus 5.1 %) and stroke (3.5% versus 4.3%) were less common with carvedilol. Heart failure (42.6% versus 44.9%), dyspnoea (9.7% versus 11.2%) and peripheral oedema (2.6% versus 3.7%) occurred less frequently with carvedilol. No consistent differences existed with regard to bradycardia or heart block. Hypotension (14.2% versus 10.5%), dizziness (12.4% versus 11.7%) and syncope 8.2% versus 6.3%) were commoner with carvedilol. Diabetes (11.1% versus 12.5%) and hypokalaemia (2.0% versus 3.2%) were less common with carvedilol. The incidence of bronchospasm (0.7% versus 0.4%) and asthma (0.5% versus 0.3%) was very low in both groups.
These differences do not take account of the fact that because of the greater mortality with metoprolol more patients in the carvedilol group were available to experience adverse events.
Conclusion: The lower number of adverse cardiovascular events with carvedilol reflects the beneficial effect on mortality. Metabolic and haemodynamic adverse events are compatible with the known different properties of these two beta-blockers.

8:45 a.m.

835-2 Carvedilol Better Protects Against Vascular Events Than Metoprolol in Heart Failure: Results From COMET

Willem J. Remme, John G. Cleland, Andrea Di Lenarda, Peter Hanrath, Beatrix Lutiger, Michel Komajda, Marco Metra, Armin Scherhag, Andrew Charlesworth, Christian Torp-Pedersen, For the COMET Investigators, STICARES - Cardiovascular Institute, Rhoon, The Netherlands, Bispebjerg Hospital, Copenhagen, Denmark

Background: In the COMET study carvedilol (C) had a significantly greater benefit on survival than metoprolol (M) in patients with NYHA class II-IV heart failure (HF), with a 20% reduction for cardiovascular (CV) mortality (RR 0.80 ;95% CI 0.7-0.9, p=0.0004). Here, we report the differentiation of CV death and the possible contribution of vascular event reduction to the beneficial effect of carvedilol.
Methods: 3029 patients with NYHA class II-IV HF, due to ischemic (51-54%) or idiopathic cardiomyopathy (44%) were randomized to C (n=1511) or M (n=1518) and followed-up double-blind for 58 months. Baseline characteristics and primary outcomes have been reported. Mode of deaths was adjudicated centrally. CV death included sudden, worsening HF, stroke and other CV death. Hospitalizations for myocardial infarctions were based on pre-specified criteria. Data provided are in the intention-to-treat population.
Results: Sudden death and death due to worsening HF were reduced in C compared to M (RR 0.81, CI 0.68-0.97 p=0.02, and RR 0.83, CI 0.67-1.02 p=0.07 respectively).
Myocardial infarctions were reported in 69 C and 94 M patients (RR 0.71, CI 0.52-0.97, p=0.03). Of these, 21 and 36 lead to death in C and M respectively. CV death or non-fatal myocardial infarction combined were reduced by 19% in C, compared to M (RR 0.81, CI 0.72-0.92, p=0.0007). A stroke occurred in 65 C and 80 M patients (RR 0.79, CI 0.57-1.10). C significantly reduced stroke deaths, 13 C versus 38 M (RR 0.33, CI 0.18-0.62,